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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,140	09/27/2000	Gary Kruh	FCCC 98-02	5331

110 7590 02/13/2003

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/647,140	Kruh et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 21, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above, claim(s) *8-44, 52-55, and 59* is/are withdrawn from consideration.

5) ☒ Claim(s) *1-3 and 5* is/are allowed.

6) ☒ Claim(s) *4, 6, and 56-58* is/are rejected.

7) ☒ Claim(s) *7 and 45-51* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-7, 45-51 and 56-58, in Paper No. 15 is acknowledged. The traversal is on the ground(s) that no lack of unity was identified in written opinion issued 4-13-00, and groups I, III, VII and X have unity of invention because they are all MOAT proteins having nucleotide binding folds containing Walker A and B binding sites and a C-terminal hydrophobic domain having membrane spanning helices. Applicants further contend for the same argument that groups II, IV, VIII, XI, groups V, VI, IX, XII, and groups XIII-XVI all have unity of invention. This is not found persuasive because they are drawn to different products having different chemical structures, physical properties and biological functions and no lack of unity identified in written opinion issued 4-13-00 is irrelevant to the present restriction requirement. Groups I, III, VII and X represent different genes having different nucleotide sequences (at least 30% identity) and encoding different proteins having different biological functions. Although these proteins have putative nucleotide binding folds and membrane spanning hydrophobic helices, they are different proteins having different amino acid sequences and different biological functions, and they have different tissue expression patterns and can transport different anions. Thus, groups I, III, VII and X do not share common special technical feature and do not relate to a single general inventive concept under PCT Rule 13.1. Similarly, groups II, IV, VIII, XI, groups V, VI, IX, XII, and groups XIII-XVI do not relate to a single general inventive concept under PCT Rule 13.1 for the same reasons.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 8-44, 52-55 and 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

Claims 1-59 are pending and claims 1-7, 45-51 and 56-58 are under consideration.

It should be noted that since Applicants elect MOAT-B (SEQ ID Nos. 1 and 2) for examination, only SEQ ID No. 1 would be examined by examiner for the claimed invention, e.g. claims 46-51 and 56-58.

Priority

3. If applicant desires priority under 35 U.S.C. 119(e) or 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date

of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c).A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Specification

4. The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, **apart from any other text**.

5. The disclosure is objected to because of the following informalities: The protein sequences in Figure 1 and Figure 2A should have a sequence identifier either in the figures or in "Brief Description of the Drawings".

Appropriate correction is required.

Claim Objections

6. Claims 49-51, 57 and 58 are objected to because of the following informalities: Since claims 49-51 depend on the host cell of claim 48, the phrase "A host cell" in claims 49-51 should be changed to "**The** host cell". Similarly, the phrase "A method" in claims 57 and 58 should be changed to "**The** method". Appropriate correction is required.

7. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 1 and 7 both read on an isolated nucleic acid molecule having the sequence of SEQ ID No. 1. They are duplicate claims.

8. Claims 45-51 and 56-58 are objected to because of the following informalities: The elected invention is nucleic acid molecule comprising SEQ ID No. 1 and its use. Claims 45-51 and 56-58 recite SEQ ID Nos. 3, 5 and 7, which are not elected invention. Therefore, the claims should be amended to recite only SEQ ID No. 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 4 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "The DNA molecule of claim 2, which is a gene comprising introns and exons" in claim 4 is vague and renders the claim indefinite. Claim 2 reads on a DNA molecule **having** the sequence of SEQ ID No. 1. The terms "having" and "comprising" both are open and interchangeable and the terms mean the DNA molecule would have exact sequence of SEQ ID No. 1 and nucleotide sequence adding to 3' and/or 5' end of SEQ ID No. 1. Since SEQ ID No. 1 is a **cDNA** molecule that does not have any intron sequence, it is unclear how the DNA molecule of claim 2 could be a gene comprising introns and exons.

The phrase "amino acid sequence encoded by natural allelic variants of said sequence" in claim 6 is vague and renders the claim indefinite. Claim 1 reads on nucleic acid having the sequence of SEQ ID No. 1, therefore, said nucleic acid would have exact sequence of SEQ ID No. 1 and nucleotide sequence adding to 3' and/or 5' end of SEQ ID No. 1. The amino acid sequence encoded by SEQ ID No. 1 is SEQ ID No. 2. It is unclear how the sequence of SEQ ID No. 1 could encode allelic variants of SEQ ID No. 2.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on a nucleic acid molecule comprising nucleotide sequence encoding amino acid sequence encoded by natural variants of SEQ ID No. 1. The specification only discloses a polynucleotide sequence of SEQ ID No. 1 and the amino acid sequence (SEQ ID No. 2) encoded by SEQ ID No. 1. The claims encompass any modified SEQ ID No. 1 sequence having substitution, addition and deletion on the nucleotide sequence of SEQ ID No. 1. The claims read on adding unknown nucleotide sequence at 5', 3' ends and/or within the nucleotide sequence of SEQ ID No. 1, or deleting or substituting the nucleotide sequence of SEQ ID No. 1.

The claims encompass various nucleic acid molecules encoding a genus of numerous structural variants of the amino acid sequence of SEQ ID No. 2, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features that contribute to the biological function of the variant proteins. There is no evidence of record that the disclosed putative nucleotide binding folds or any other putative consensus domain in MOAT-B protein contributes to the anion transporting activity of MOAT proteins. Structural features that could distinguish compounds in

the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the amino acid sequence of SEQ ID No. 2 as disclosed in the present application is insufficient to describe the genus. Therefore, the nucleotide sequence of SEQ ID No. 1 encoding the amino acid sequence of SEQ ID No. 2 is insufficient to describe the claimed nucleic acid molecules.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed nucleic acid molecules. Thus, it is concluded that the written description requirement is not satisfied for the nucleic acid molecules as claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate

written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed nucleotide sequence of SEQ ID No. 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

13. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule comprising the sequence of SEQ ID No. 1, does not reasonably provide enablement for any nucleic acid molecule having allelic variant sequence of SEQ ID No. 1 or encoding structural variants of SEQ ID No. 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims read on a nucleic acid molecule comprising nucleotide sequence encoding amino acid sequence encoded by natural variants of SEQ ID No. 1. The specification only discloses a polynucleotide sequence of SEQ ID No. 1 and the amino acid sequence (SEQ ID No. 2) encoded by SEQ ID No. 1. The claims encompass any modified SEQ ID No. 1 sequence having substitution, addition and deletion on the nucleotide sequence of SEQ ID No. 1. The claims read on adding unknown nucleotide sequence at 5', 3' ends and/or within the nucleotide sequence of SEQ ID No. 1, or deleting or substituting the nucleotide sequence of SEQ ID No. 1.

The claims encompass various nucleic acid molecules encoding a genus of numerous structural variants of the amino acid sequence of SEQ ID No. 2, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features that contribute to the biological function of the variant proteins. The specification also fails to provide adequate guidance and evidence whether the structural variants of SEQ ID No. 2 (MOAT-B) encoded by the claimed nucleic acid molecules would have the MOAT mediated transporter activity.

It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar or higher activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and

sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of the lack of detailed information regarding the structural and functional requirements of the amino acid sequence of SEQ ID No. 2 and its variants, and the unpredictability of protein function from mere amino acid sequence, it would be unpredictable whether the proteins encoded by the claimed nucleic acid molecules would have MOAT mediated transporter activity. In view of such, one skilled in the art at the time of the invention would not know how to use the claimed nucleic acid molecules encoding various structural variants of SEQ ID No. 2, and numerous known and unknown proteins.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require a skilled artisan at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

14. Claims 56-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 56-58 are directed to a method for screening a test compound for inhibition of MOAT mediated transport comprising providing a host cell expressing MOAT-encoding nucleic acid sequence of SEQ ID No. 1, contacting said host cell with a compound suspected of inhibiting MOAT-mediated transporter activity and assessing inhibition of transport mediated by said compound by measuring restoration of anticancer drug sensitivity or a reduction of transporter mediated cellular efflux of anticancer agents.

The claims encompass using any host cell having nucleotide sequence of SEQ ID No. 1 under the control of any promoter for screening a test compound that inhibits MOAT mediated transport *in vitro* or *in vivo*. The specification fails to disclose any method for screening a test compound for inhibition of MOAT mediated transport comprising contacting the host cell set forth above with a compound suspected of inhibiting MOAT-mediated transporter activity and

assessing inhibition of transport mediated by said compound by measuring restoration of anticancer drug sensitivity or a reduction of transporter mediated cellular efflux of anticancer agents.

The specification fails to provide adequate guidance and evidence for how to screen a test compound with any type of host cell having the nucleotide sequence of SEQ ID No. 1 under the control of various promoters, including endogenous MOAT-B promoter and any other promoter that does not initiate expression of MOAT-B in naturally occurring cells. There is no evidence of record that MOAT-B protein can mediate cellular efflux of any anticancer agent in a host cell and inhibition of MOAT-B protein activity could restore anticancer drug sensitivity. One skilled in the art at the time of the invention would not know how to use the MOAT-B gene for screening test compound that inhibits MOAT mediated anion transport according to the claimed method.

The specification also fails to provide adequate guidance and evidence that a test compound, which inhibits MOAT-B gene expression under the control of a promoter other than the natural MOAT-B promoter in a host cell, could also inhibit MOAT-B gene expression under the control of its natural promoter in a host cell. When a test compound inhibits MOAT-B gene expression under the control of a promoter other than the natural MOAT-B promoter, the test compound inhibits the activity of said promoter and it is not necessarily that said compound would also inhibit the activity of the natural MOAT-B promoter in a host cell *in vitro* or *in vivo*. Restoration of anticancer drug sensitivity or reduction of transporter mediated cellular efflux of anticancer agents would only indicates inhibition of the promoter activity by the test compound,

and said test compound would not necessarily inhibit MOAT-B protein activity in a naturally occurring cell *in vitro* or *in vivo*. Therefore, one skilled in the art at the time of the invention would not know how to use the claimed method to screen test compound that inhibits MOAT mediated transport.

The specification fails to provide adequate guidance and evidence how to screen a test compound that inhibits MOAT mediated transport by using a host cell having the nucleotide sequence of SEQ ID No. 1 under the control of various promoters *in vivo*. The specification also fails to provide adequate guidance and evidence how to measure the restoration of anticancer drug sensitivity or reduction of transporter mediated cellular efflux of anticancer agents *in vivo*. The biological environment *in vivo* is very different from the biological environment *in vitro*. The factors in *in vitro* environment were well controlled, such as the type of medium, the ingredients of the medium, the temperature of the medium and the type of the container used. However, there are various unknown bioactive factors that can not be controlled *in vivo* and these bioactive factors interact with each other and with various regulatory elements. It was known in the art that a gene which is expressed *in vitro* is not necessarily to be expressed *in vivo* in various cell types because the microenvironment *in vitro* is different from the microenvironment *in vivo*. The interplay of various different factors could lead to different expression patterns of the MOAT-B gene *in vivo*. Thus, it was unpredictable at the time of the invention whether a test compound that inhibits MOAT mediated transport *in vitro* can also inhibit MOAT mediated transport *in vivo*.

For the reasons discussed above, one skilled in the art at the time of the invention would have to engaged in undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

15. Claims 4, 6 and 56-58 are rejected. Claims 45-51 are objected. Claims 1-3 and 5 are in condition for allowance. Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S Chen